Critical Care

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Impact on fluid balance of an optimized restrictive strategy targeting non-resuscitative fluids in intensive care patients with septic shock: a single-blind, multicenter, randomized, controlled, pilot study

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Abstract

Background In septic shock, the classic fluid resuscitation strategy can lead to a potentially harmful positive fluid balance. This multicenter, randomized, single-blind, parallel, controlled pilot study assessed the effectiveness of a restrictive fluid strategy aiming to limit daily volume.

Methods Patients 18–85 years' old admitted to the ICU department of three French hospitals were eligible for inclusion if they had septic shock and were in the first 24 h of vasopressor infusion. Exclusion criteria were acute kidney injury requiring renal replacement therapy, end stage chronic kidney disease, and severe malnutrition. Patients were electronically randomized 1:1 to either an optimized fluid restriction (reducing fluid intake as much as possible in terms of maintenance fluids and fluids for drug dilution during the first 7 days) or standard fluid strategy. The primary outcome was cumulative fluid balance (ml/kg) in the first 5 days. Patients and statisticians were blinded to group arm, but not clinicians.

Results Between September 2021 and February 2023, 1201 patients were screened and 50 included, with two in the control group withdrawing, thus 48 patients were analyzed (24 in each group). In the first 5 days, the optimized restrictive strategy and control groups received 89.7 (IQR 35; 128.9) and 114.3 (IQR 78.8; 168.5) ml/kg of fluid, respectively (mean difference: 35.9 ml/kg [0.0; 71.8], $p=0.0506$). After 5 days, the median cumulative fluid balance was 6.9 (IQR − 13.7; 52.1) and 35.0 (IQR − 7.9; 40.2) ml/kg in the optimized restrictive strategy and control groups, respectively (absolute difference 13.2 [95%CI − 15.2; 41.6], $p=0.42$). After 28 days, mortality and the numbers of days alive without life support were similar between groups. The main adverse events were severe hypernatremia in 1 and 2 patients in the fluid restriction strategy and control groups, respectively, and acute kidney injury KDIGO 3 in 4 and 7 patients in the fluid restriction strategy and control groups, respectively.

Conclusions In ICU patients with septic shock, an optimized restrictive fluid strategy targeting hidden fluid intakes did not reduce the overall fluid balance at day 5.

Trial registration ClinicalTrials.gov identifier NCT04947904, registered on 1 July 2021.

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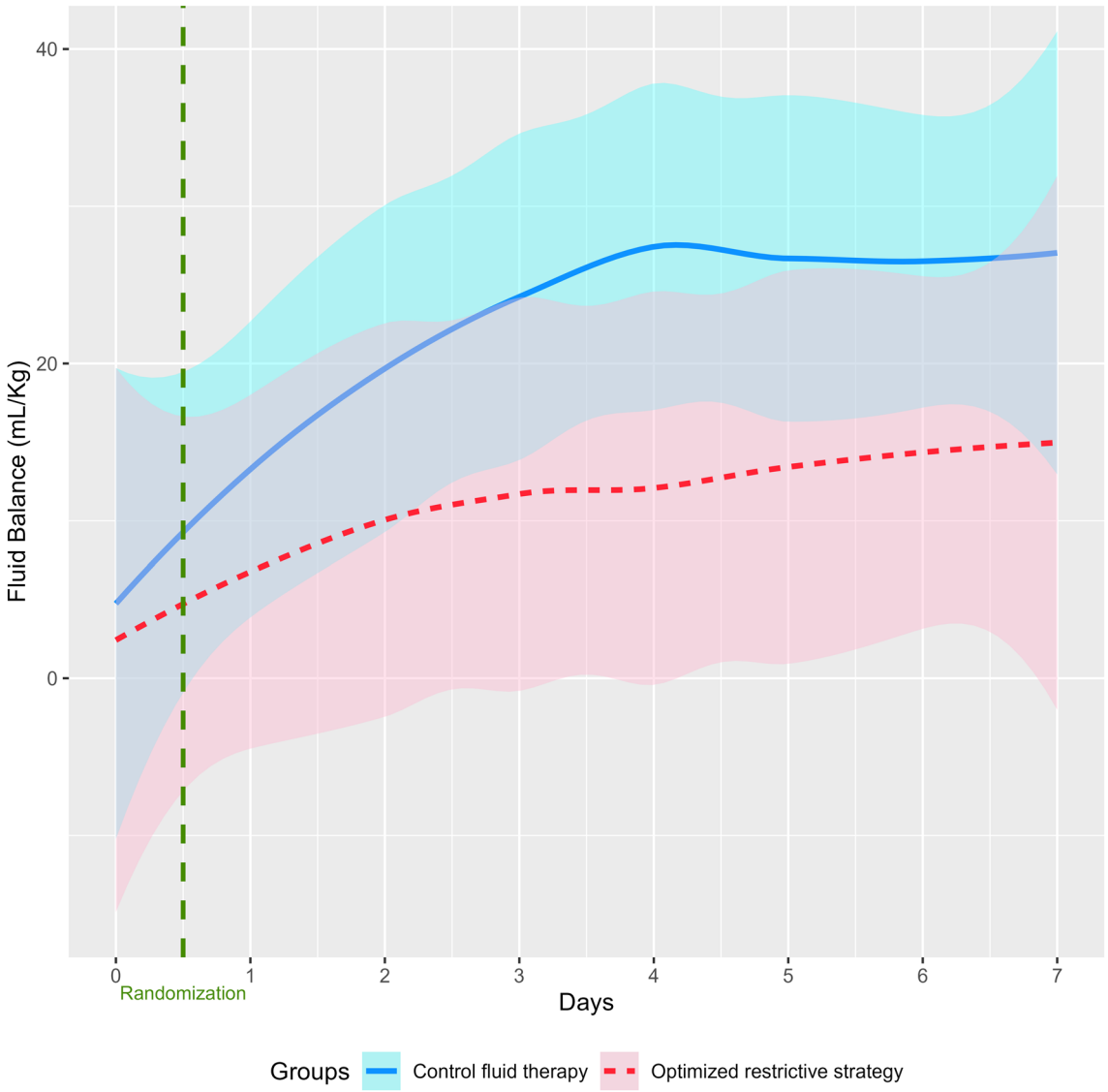
Keywords Fluid balance, Septic shock, Intensive care unit, Restrictive strategy

Graphical Abstract



Background

Sepsis is the cause of nearly 30% of hospitalizations in the intensive care unit (ICU), with a mortality rate about 40% 28 days after admission [1]. Fluid resuscitation therapy is a cornerstone of the initial management of patients with septic shock but can lead to fluid overload. A positive fluid balance in the first few days after admission to an intensive care unit (ICU) is related with negative outcome and an increased risk of mortality [2–5], in particular if sepsis is combined with acute respiratory distress syndrome [3, 4] and acute renal failure [2]. Patients with septic shock can receive large volumes of fluids, of up to 25 L in three days [6, 7]. Interestingly, the volume of resuscitation fluids constitutes only one-third of the total fluid intake received in the acute phase of septic shock [8]. Maintenance/replacement fluids, called "creep fluids" or "hidden fluid intakes", include the fluids to perfuse

electrolytes, the small volumes to keep venous lines open (saline or glucose 5%), fluids for drug delivery, and parenteral and enteral nutrition. One retrospective study including 14,654 ICU patients reported that maintenance/replacement fluids accounted for over 55% of fluid intake during the first five days in the ICU, with significant sodium and chloride loads [8]. Another retrospective study performed in 10 ICUs and involving 400 patients, confirmed that maintenance and dilution fluids accounted for more than 50% of fluids infused during the first three ICU days [9]. Furthermore, the fluid balance in the first three days was independently associated with 30-day mortality.

Several randomized clinical trials (RCT) have investigated the benefits of different fluid restriction strategies, targeting uniquely or mostly resuscitative fluids. When applied in the acute phase of the management of patients with septic shock, these strategies resulted in small differences in fluid intake and no difference in survival [10–13].

Studies are needed focusing on a restrictive strategy targeting non-resuscitative fluid input to optimize fluid balance in patients with septic shock. We designed a pilot randomized controlled trial (OPTIFLUID) studying the impact of an optimized restrictive strategy targeted at reducing all fluid infusions other than resuscitative fluids. The primary objective was to assess the fluid balance after the first 5 days of resuscitation in ICU patients with septic shock. Secondary outcomes were fluid balance, body weight variation, use of diuretics, death, organ failure free days and length of stay.

Methods

Trial design and oversight

OPTIFLUID is a multicenter, single-blind, randomized, parallel, controlled, pilot trial. Patients were recruited between September 20, 2021, and February 25, 2023 in ICUs in the university hospitals of Nîmes and Dijon, and the general hospital of Alès, France. The study was approved by the Comité de Protection des Personnes Sud-Méditerranée II, France (number 2020-A01952-37). Written informed consent was obtained from patients or their legal surrogates either before randomization or as soon as possible thereafter [14]. The trial was funded by Nîmes University Hospital, France.

Patients

Patients between 18 and 85 years' old were eligible if they were admitted to the ICU in the early phase of septic shock (within 24 h after the start of vasopressor therapy). Septic shock was defined as suspected or confirmed infection, a plasma lactate level of ≥ 2 mmol/L and ongoing infusion of a vasopressor agent [1]. Exclusion criteria were acute kidney injury requiring renal replacement therapy within the next 24 h, end stage chronic kidney disease, and severe malnutrition with body mass index < 18. Detailed inclusion and exclusion criteria are presented in Supplementary Table S1.

Randomization and blinding

Randomization was performed using a centralized, computer-generated allocation sequence. Eligible patients were randomly assigned in a 1:1 ratio, (in permuted blocks of 2), to receive the optimized restrictive strategy or standard fluid therapy (control group).

Treatment group assignments were not masked for clinicians or investigators but were concealed from patients and the statisticians.

Interventions

All patients were treated according to the recommendations of the Surviving Sepsis Campaign [15]. During the first 7 days of septic shock, fluid infusion was given following an optimized restrictive strategy or standard fluid therapy (control group). To calculate the dose of fluids administered, we always used the patient's weight on admission to ICU. Trial staff (physicians, clinical pharmacists and nurses) were trained before inclusion began. The coordinating investigator and the clinical pharmacist were available throughout the inclusion period to help the investigators comply with the protocol.

Optimized restrictive strategy (experimental group)

A restrictive fluid protocol was applied upon inclusion on Day 1 and continued for the first 7 days of hospitalization in the ICU. Clinicians were instructed to reduce fluid intake as much as possible in terms of maintenance fluids, drug dilution and artificial nutrition. The management of resuscitative fluids, defined as fluids prescribed to optimize blood volume in the treatment of shock, was not modified by the protocol, and was left to the judgement of clinicians according to their usual monitoring strategy (cardiac ultrasound, pulse index continuous cardiac output, right heart catheterization, central venous pressure, etc.). For drug dilutions, the clinicians consulted charts (Supplementary Table S2) showing the maximum possible concentrations for the drugs most frequently used in ICU, particularly antibiotics, based on literature data [16]. For artificial nutrition, the intravenous route was discouraged before Day 5 [17]. For enteral nutrition, the protocol provided for the use of a hypercaloric (2 kcal/ml) high protein product, with a total caloric objective

of 20 kcal/kg per day in the acute phase and 30 kcal/kg per day after stabilization [18]. Intravenous fluids other than those needed to dilute drugs and electrolytes were prohibited, and only 2 ml/hour of saline or glucose were authorized to maintain veins. A clinical pharmacist intervened daily to check adherence to the fluid restriction protocol. If the restrictive strategy induced hypovolemia and/or biological abnormalities (sodium, potassium, chloride, etc.), the treating physician could increase fluid therapy in accordance with the protocol's recommendations. The fluid restriction strategy did not involve the systematic administration of diuretics.

Standard fluid strategy (control group)

The choice of the volume of fluid intake other than resuscitative fluids was left to the physician's discretion, based on usual practices: usually between 500 and 2000 ml/day of maintenance volumes. The dilutions of drugs were those officially planned at the time of marketing approval, enteral artificial nutrition (isocaloric, high protein) was initiated as soon as possible, with the same rules for parenteral nutrition if the caloric target could not be reached with enteral nutrition.

Diuretics were authorized in both groups at the judgement of the clinicians according to the needs of the patients, but were not recommended as long as patients had high dose vasopressors.

Outcomes

The primary outcome was fluid balance in the first 5 days. Secondary outcomes were fluid balance at Day 3, 5 and 7; body weight variation at Day 5 and 7; death from any cause at Day 7 and 28; the number of days alive without life support and without organ failure (SOFA = 0) at Day 28; the number of days alive without vasopressors, mechanical ventilation and renal replacement therapy at Day 28; the number of days alive outside the ICU at Day 28; the ICU and hospital length of stay; and the use of diuretics (cumulative dose administered over 7 days). Finally, in addition to unexpected adverse events, predefined adverse events during the entire ICU stay were collected, specifically metabolic (mild and severe hypernatremia, hyponatremia), renal (hyperkalemia, Acute Kidney Injury KDIGO2 and 3), and nutritional (hypoglycemia, stage 3 pressure sores acquired in the ICU); cumulative insulin dose over 7 days) complications potentially related to the restrictive fluid strategy; norepinephrine doses and lactate levels over 7 days.

Statistical analysis

Considering that "hidden" fluid intake constitutes 55% of total intake by patients, we estimated that a restrictive strategy would lead to a relative 40% reduction in fluid balance, conferring a significant clinical impact. Assuming a mean fluid balance of 70 mL/kg in the control group [6–8], 40 mL/kg in the experimental group and a standard deviation of 35 mL/kg, we estimated that 44 patients (22 per group) were needed to guarantee 80% statistical power with a two-sided alpha risk of 5%. This number was increased by 10% to take into account any deaths between Day 1 and Day 5. The total number of subjects required was therefore 50 patients (25 per group).

The primary endpoint, fluid balance at Day 5 (ml/kg), was compared between groups using a Mann–Whitney test via intention-to-treat analysis. A second per-protocol analysis was performed, where only patients who had been depleted for at least 5 days were considered, as well as a sensitivity analysis in which we excluded patients with bleeding (defined as more than 2 units of blood transfusion in the same day). Categorical variables are expressed as numbers and percentages; continuous variables are expressed as means and standard deviations or medians and interquartile ranges (IQR) as appropriate. Quantitative variables were compared between two groups using a Student's t test if the variable had a normal distribution, or a Wilcoxon Mann Whitney otherwise. The mean difference between the two groups was also calculated with the 95% confidence interval. For categorical variables, either the Chi^2 test or Fisher's exact test were used and the percentage difference between the experimental and control group was also calculated, as was the associated relative risk with the 95% confidence interval. The length of ICU and hospital stay, and the number of days free of mechanical ventilation, vasopressors, and renal-replacement therapy are expressed as medians and IQR and were compared using the Mann–Whitney test. We evaluated safety by calculating the percentage of patients in the two groups presenting metabolic, renal and nutritional adverse events; percentages were compared with the use of appropriate tests. The significance level was set at 0.05 for all analyses.

Analyses were performed with SAS Enterprise Guide software, version 7.1.

Study protocol

The trial protocol, which includes the statistical analysis plan, was registered on ClinicalTrials.gov with the identifier NCT04947904.

For evaluation of patient safety, this trial has been registered with France National Agency of Drug Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM).

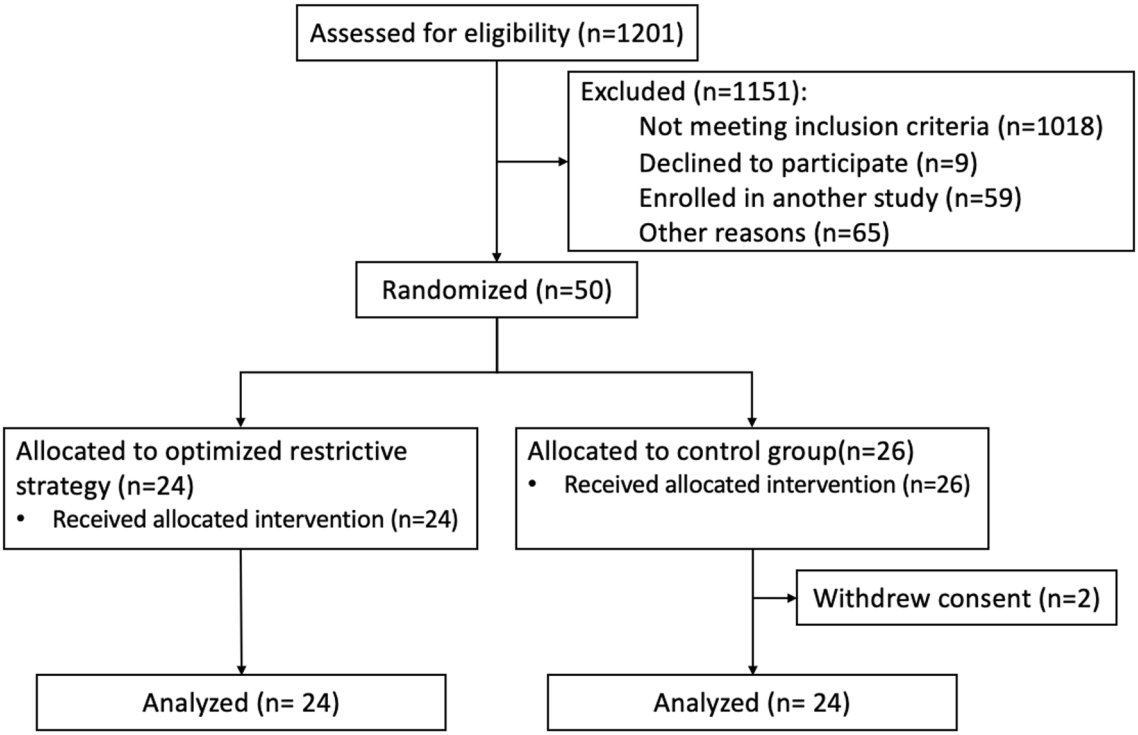


Fig. 1 Flow chart

Trial data were monitored at the sites by independent monitors and monitored centrally by staff at the coordinating centre. The first and the last author wrote the first draft of the manuscript, which was reviewed by all the authors. Statistical analyses were performed by the trial statistician in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. The authors vouch for the accuracy and completeness of the reported analyses and for the fidelity of the trial to the protocol.

Results

Population

Between September 2021 and February 2023, 1201 patients were assessed for eligibility. Fifty patients were randomized, with two in the control group withdrawing consent, leading to 24 analyzable patients per group (Fig. 1). Patients had an average age of 68.3 ± 10.2 years and an average SAPSII score of 56.5 ± 19.2. Patient characteristics at baseline are shown in Table 1. Patient characteristics at baseline were well balanced between the two groups, except for serum creatinine, which was higher in the intervention group (Table 1). During the 28-day trial period, patients in both intervention groups remained in the ICU for a median of 5 days after randomization (IQR, 3 to 10 days).

Fluid intervention

The median cumulative volumes of fluids administered in the first 5 days were 89.7 (IQR 35; 128.9) and 114.3 (78.8; 168.5) ml/kg in the optimized restrictive strategy and control group, respectively (mean difference 35.9 [95%CI − 0.0; 71.8], $p=0.0506$) (Table 2). The 7-day median cumulative volumes of fluids administered were 98.8 (IQR 35.0; 184.6) and 123.8 (IQR 78.8; 217.5) ml/kg in the optimized restrictive strategy and control groups, respectively (mean difference 37.5 [95%CI − 16.5; 91.5], $p=0.17$).

Concerning fluid administration, resuscitative fluid volumes were similar in both groups at Day 5 and Day 7 (Table 2). For the non-resuscitative fluids, vein maintenance fluids were lower in the optimized restrictive strategy group at Day 5 (mean difference 20.0 ml/kg [95%CI 6.4; 33.6], $p<0.01$) and Day 7 (mean difference 21.7 ml/kg [1.4; 42.1], $p<0.01$), whereas other non-resuscitation fluids were similar between groups (Table 2 and Supplementary Table S3, S4 and S5).

Protocol adherence

There were no violations of fluid protocol in the optimized restrictive strategy group, but total fluid volume at Day 5 and Day 7 was lower than expected in the control group (Table 2).

Table 1 Patient characteristics at baseline

Characteristics	Optimized restrictive strategy group (N = 24)	Control group (N = 24)
Mean age (SD)—year	69.5 (± 8.8)	67.0 (± 11.5)
Male sex—no. (%)	12 (50.0)	13 (54.2)
Mean body weight (SD)—kg	67.7 (± 14.8)	73.4 (± 16.6)
Mean body mass index (SD)	24.5 (± 5.1)	26.0 (± 6.7)
Coexisting condition—no. (%)		
Hematologic or metastatic cancer	7 (29.2)	8 (33.3)
Ischemic heart disease or heart failure	3 (12.5)	4 (16.7)
Chronic hypertension	14 (58.3)	11 (45.8)
Chronic kidney disease	1 (4.2)	2 (8.3)
Cirrhosis	2 (8.3)	0 (0)
Diabetes mellitus	8 (33.3)	5 (20.8)
Median time from ICU admission to randomization (IQR)—days	1.0 (0.0; 1.0)	1.0 (0.0; 1.0)
Mean SAPSII score (SD)	54.5 (± 21.9)	58.5 (± 16.4)
Referral department—no. (%)		
Emergency department or prehospital	12 (50.0)	12 (50.0)
Hospital ward	12 (50.0)	12 (50.0)
Origin of infection—no. (%)		
Gastrointestinal	7 (29.2)	8 (33.3)
Pulmonary	12 (50.0)	11 (45.8)
Urinary tract	1 (4.2)	4 (16.7)
Skin or soft tissue	1 (4.2)	1 (4.2)
Other	4 (16.7)	2 (8.3)
Blood values		
Median highest plasma lactate (IQR)—mmol per liter	2.1 (1.4; 3.7)	2.3 (1.5; 3.0)
Median highest plasma creatinine (IQR)—µmol per liter	94.5 (67.5; 133.5)	170.5 (75.0; 231.0)
Mean serum sodium level (SD)—µmol per liter	137.0 (± 4.2)	137.6 (± 4.5)
Mean serum potassium level (SD)—µmol per liter	3.9 (± 0.7)	3.9 (± 0.5)
ICU interventions		
Median highest dose of norepinephrine (IQR)—µg/kg/min	0.4 (0.2; 1)	0.5 (0.3; 0.8)
Median volume of IV fluid 24 h before randomization (IQR)—ml	30.3 (15.2; 37.5)	21.8 (9.9; 38.7)
Use of respiratory support—no. (%)	16 (66.7)	14 (58.3)
Median lowest PaO2/FiO2 ratio (IQR)	207 (143; 277)	216 (158; 269)

Primary outcome

At Day 5, the median cumulative fluid balance was 6.9 (IQR − 13.7; 52.1) versus 35.0 (IQR − 7.9; 40.2) ml/kg in the optimized restrictive strategy and control groups, respectively (absolute difference 13.2 [95%CI − 15.2; 41.6], $p = 0.42$) (Table 2, Fig. 2A). Sensitivity analysis excluding patients with hemorrhage requiring blood transfusions gave similar results (Table S6).

Secondary outcomes

At Day 3, the median cumulative fluid balance was 9.8 (IQR − 8.0; 38.8) and 24.7 (IQR 2.2; 37.7) ml/kg in the optimized restrictive strategy and control group, respectively (absolute difference 13.8 [95%CI − 6.9; 34.4], $p = 0.19$) (Table 3, Fig. 1A).

At Day 7, the median cumulative fluid balance was 12.6 (IQR − 19.9; 58.7) and 26.4 (IQR 16.3; 39.8) ml/kg in the optimized restrictive strategy and control groups, respectively (absolute difference 12.5 [95%CI − 24.2; 49.3] $p = 0.72$). There was no significant difference in body weight variation at Day 3, 5 and 7 (Fig. 2B). There was no statistical difference in survival, organ failure free-days, or ICU and hospital length of stay (Table 3).

Adverse events

We found no difference in the predefined adverse events, metabolic disorders, renal function, or nutritional issues (Table 4). Mild hypernatremia (Na 146–150 mmol/L) was observed in 7 patients (29%) in the optimized restrictive strategy group and 10 (42%) in the control group, relative

Table 2 Median Cumulative Fluid Volumes in ICU during intervention

Fluid Volumes	Optimized restrictive strategy group	Control Group	Mean difference	*p*-value
Median (IQR)—ml/Kg of admission body weight	(N = 24)	(N = 24)		
Total fluid intake volume after 5 days	89.7 (35; 128.9)	114.3 (78.8; 168.5)	35.9 [0.0; 71.8]	0.0506
Total fluid intake volume after 7 days	98.8 (35.0; 184.6)	123.8 (78.8; 217.5)	37.5 [– 16.5; 91.5]	0.17
Intravenous fluid volume after 5 days				
Resuscitative fluids				
Crystalloids*	8.3 (0.0; 16.4)	7.5 (0.0; 15.0)	2.8 [– 5.1; 10.7]	0.80
Albumin	0.0 (0.0; 0.0)	0.0 (0.0; 2.7)	1.2 [– 1.4; 3.8]	0.21
Non-Resuscitative fluids				
Transfusions	0.0 (0.0; 0.0)	0.0 (0.0; 1.4)	2.5 [– 0.6; 5.5]	0.38
Blood derivatives	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	– 0.1 [– 1.7; 1.6]	0.96
Vein maintenance	7.2 (3.0; 12.5)	24.6 (14.9; 46.2)	20.0 [6.4; 33.6]	< 0.001
Ion dilution	1.3 (0.3; 2.9)	1.4 (0.6; 3.2)	0.5 [– 1.1; 2.2]	0.56
Drug dilution	35.3 (12.2; 48.7)	37.0 (20.0; 59.4)	4.2 [– 11.4; 19.8]	0.59
Fluids to treat hypernatremia[#]	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.8 [– 0.6; 2.3]	0.54
Parenteral nutrition	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.8 [– 7.0; 8.7]	0.75
Enteral/oral fluid Volume after 5 days				
Enteral nutrition	0.0 (0.0; 19.6)	0.0 (0.0; 21.0)	– 0.1 [– 8.2; 7.9]	0.96
Water in nasogastric tube	2.0 (0.0; 11.0)	1.6 (0.0; 12.0)	2.4 [– 3.9; 8.8]	0.96
Oral fluid intake	2.3 (0.0; 3.4)	0.9 (0.0; 3.2)	0.8 [– 2.7; 4.3]	0.49
Intravenous fluid volume after 7 days				
Resuscitative fluids				
Crystalloids*	9.3 (0.0; 20.3)	8.4 (0.0; 15.0)	1.5 [– 6.7; 9.6]	0.93
Albumin	0.0 (0.0; 0.0)	0.0 (0.0; 2.7)	1.2 [– 1.4; 3.8]	0.21
Non-Resuscitative fluids				
Transfusions	0.0 (0.0; 0.0)	0.0 (0.0; 7.6)	3.4 [– 0.3; 7.0]	0.19
Blood derivatives	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	21.7 [1.4; 42.1]	0.57
Vein maintenance	9.4 (3.0; 17.8)	26.2 (16.9; 49.0)	21.7 [1.4; 42.1]	< 0.01
Ion dilution	1.4 (0.3; 3.3)	1.4 (0.6; 3.6)	0.5 [– 1.3; 2.2]	0.66
Drug dilution	39.4 (12.2; 58.5)	38.5 (20.0; 77.3)	4.7 [– 15.6; 25.1]	0.63
Fluids to treat hypernatremia[#]	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.7 [– 0.8; 2.3]	0.54
Parenteral nutrition	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.0 [– 9.3; 9.3]	> 0.99
Enteral/oral fluid Volume after 7 days				
Enteral nutrition	5.1 (0.0; 32.4)	0.0 (0.0; 22.9)	– 1.4 [– 14.3; 11.4]	0.58
Water in nasogastric tube	2.3 (0.0; 13.1)	1.6 (0.0; 19.2)	4.7 [– 3.3; 12.7]	0.87
Oral fluid intake	2.5 (0.0; 5.8)	0.9 (0.0; 4.7)	0.2 [– 3.5; 3.9]	0.44
Total fluid output after 5 days	67.9 (33.0; 118.4)	95.5 (61.5; 131.5)	23.4 [– 6.5; 53.3]	0.12
Total fluid output after 7 days	87.0 (33.0; 167.1)	113.4 (61.5; 184.1)	25.7 [– 19.5; 70.9]	0.26
Fluid output after 5 days				
Urine output	63.3 (28.8; 115.1)	92.8 (47.8; 125.2)	18.0 [– 11.4; 47.5]	0.29
Ultrafiltration on RRT[$]	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	6.2 [– 5.5; 18.0]	0.54
Drains	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.2 [– 2.0; 2.4]	0.93
Diarrhea	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	– 0.3 [– 1.1; 0.6]	1.00
Nasogastric tube	0.0 (0.0; 5.9)	0.0 (0.0; 2.3)	– 0.8 [– 5.5; 3.9]	0.76
Fluid output after 7 days				
Urine output	64.3 (28.8; 149.7)	95.3 (47.8; 157.9)	17.8 [– 25.0; 60.6]	0.41
Ultrafiltration on RRT[$]	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	11.0 [– 8.2; 30.1]	0.95
Drains	0.0 (0.0; 0.6)	0.0 (0.0; 0.0)	– 1.9 [– 6.6; 2.8]	0.82
Diarrhea	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.1 [– 1.6; 1.7]	0.61
Nasogastric tube	0.0 (0.0; 6.2)	0.0 (0.0; 2.3)	– 1.2 [– 6.5; 4.1]	0.76

Table 2 (continued)

*(NaCl 0.9%, Ringer lactate, isotonic balanced solutions)

2.5% and 5% glucose solution

$ Renal Replacement Therapy

risk 0.7 [95%CI 0.32; 1.53], $p=0.37$. Severe hypernatremia (Na > 150 mmol/L) was observed in 1 patient (4%) in the optimized restrictive strategy group and 2 (8%) in the control group, relative risk 0.5 [95%CI 0.05; 5.15], $p=0.37$. Acute kidney injury KDIGO 2 was observed in 9 patients (37%) in the optimized restrictive strategy group and 11 patients (46%) in the control group. Median cumulative dose of diuretics administered over 7 days was similar in both groups: mg furosemide 40 mg (IQR 20; 16) in the optimized restrictive strategy group vs 60 mg (IQR 30; 320) in the control group, mean difference-32 [− 810; 746], $p=0.56$. Changes in norepinephrine doses and lactate levels during the first 7 days of ICU stay are reported in Supplementary Table S7.

Discussion

In this multicenter, single-blind, randomized, controlled, pilot trial, an optimized fluid restriction protocol to reduce "hidden fluid intakes" did not lead to a relative 40% reduction in fluid balance at Day 5 when compared with standard fluid strategy (control group). The fluid balances at Day 3, Day 5, changes in weight, number of days free of organ failure and mortality rate at Day 28 were similar in both groups.

We cannot directly compare our results to previous studies on fluid restriction because OPTIFLUID is the first study which targeted uniquely non resuscitative fluids. Recently, two large RCT [11, 19] assessed the impact of a restrictive strategy applied during the ICU stay focused on all intravenous fluids and not uniquely on resuscitative fluids. In both studies, the restrictive strategy reduced cumulative fluid balance with no effect on mortality rate.

In the CLASSIC trial, Meyhoff et al. [11] found no reduction in 90-day mortality or any other secondary outcome in septic patients. Their fluid restriction protocol focused mostly on resuscitative fluids (intravenous fluid therapy for hypoperfusion or to correct fluid losses or dehydration), with a very aggressive protocol forbidding fluids if the lactate level was lower than 4 mmol/l or in absence of oliguria. However, in a secondary post-hoc analysis this strategy did not seem to affect the time to resolution of hyperlactatemia [20].

In the POINCARE-2 trial [19], Bollaert et al. found no reduction in mortality at day 60 or in any other secondary outcome in a broad range of critically ill patients with a fluid restriction protocol based on daily weighing, salt and fluid restriction and the use of furosemide (with or without albumin) during the first two weeks of hospitalization in ICU. In this trail, a higher difference in cumulative fluid balance was obtained with large doses of furosemide and perfusions of 20% albumin. Thus, the findings were probably more dependent on medical treatment (and potential side effects) rather than on the restrictive strategy per se.

Although we were unable to demonstrate a statistically significant reduction in fluid balance, it is noteworthy that the total fluid intakes with our protocol were much lower than those of the intervention groups in previously cited fluid restriction studies [11, 19]. Notably, the fluid balance of the control group in our study was also lower than, or similar to, that of patients in the intervention group in the previously cited fluid restriction studies, without systematic administration of diuretics [11, 19, 21]. This could explain why no difference was seen in clinical outcomes or metabolic parameters such as hypernatremia, acute renal failure and issues related to nutritional intake. Promisingly, the optimized restrictive fluid strategy was not associated with notable side-effects.

Our study had several limitations. First, the infused fluid volumes in the control group were far below the ranges observed in recent trials on fluid restriction, which prevented us from demonstrating a significant difference. Possibly the intensivists in the participating centers were convinced of the benefits of the restrictive fluid strategy and inadvertently applied a fluid restrictive strategy also in the control group, explaining the non-representativeness of the control group Moreover, the differences in administered volumes were almost entirely restricted to maintenance fluids, while dilutional fluids were identical. It is possible that the doctors and the nurses at the participating centres, seeing that different dilutions with higher concentrations could be used in the intervention arm, started using the same dilutions in the control arm, which does not constitute a breach of protocol sensu stricto. An alternative explanation may be that dilutional fluids cannot be adequately minimized as many drugs require a predefined amount of fluids. Second, the physicians and nurses were not blinded to group assignment due to the individual randomization design. A randomized step-wedge cluster design would overcome this issue, but would require more centers and patients. Thirdly, renal dysfunction was more severe in the control group, both at baseline and after the intervention phase. This difference may be due to the intervention, or to the severity of the patients at the time of randomization,

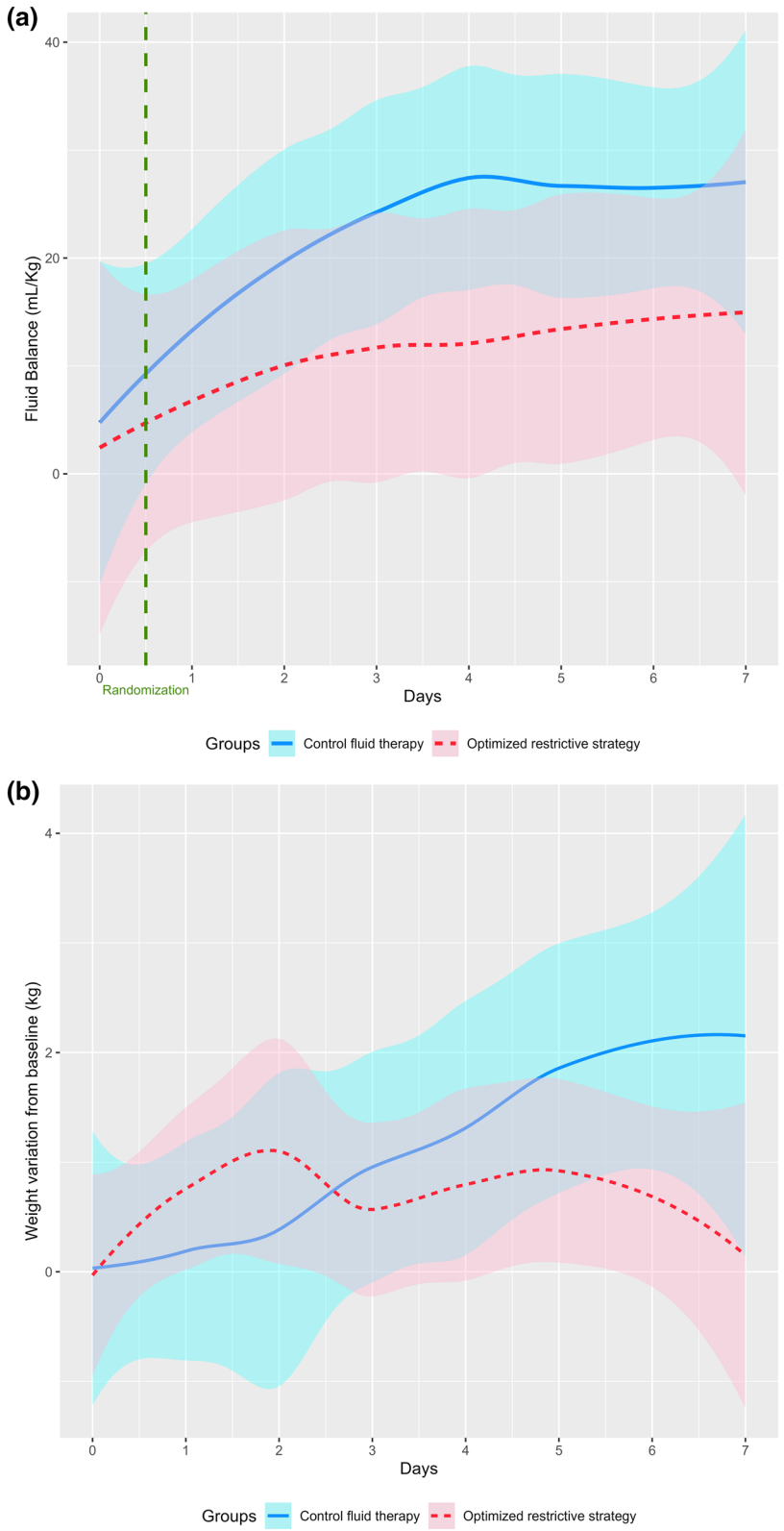


Fig. 2 **A** Cumulative fluid balance variation during intervention. **B** Weight variation from baseline during intervention

Table 3 Primary and secondary outcomes

	Optimized restrictive strategy group (n = 24)	Control group (n = 24)	Absolute difference	Relative risk	*p*-Value
Primary outcome					
Cumulative fluid balance at Day 5—Median (IQR) ml/kg of admission body weight	6.9 (– 13.7; 52.1)	35.0 (– 7.9; 40.2)	13.2 [– 15.2; 41.6]		0.42
Secondary outcomes					
Cumulative fluid balance at Day 3—Median (IQR) ml/kg of admission body weight	9.8 (– 8.0; 38.8)	24.7 (2.2; 37.7)	13.8 [– 6.9; 34.4]		0.19
Cumulative fluid balance at Day 7—Median (IQR) ml/kg of admission body weight	12.6 (– 19.9; 58.7)	26.4 (16.3; 39.8)	12.5 [– 24.2; 49.3]		0.72
Body weight variation at Day 3—Median (IQR) kg (%)	0.0 (0.01; 0.02)	0.01 (0.01; 0.04)	0.01 [– 0.02; 0.05]		0.34
Body weight variation at Day 5—Median (IQR) kg (%)	0.0 (0.01; 0.03)	0.0 (0.0; 0.0)	0 [– 0.04; 0.03]		0.84
Body weight variation at Day 7—Median (IQR) kg (%)	0.00 (0.0; 0.0)	0.0 (0.0; 0.0)	– 0.01 [– 0.04; 0.03]		0.83
Death by Day 7—N (%)	4 (16.7)	5 (20.8)	– 0.04 [– 0.26; 0.18]	0.8 [0.24; 2.62]	1.00
Death by Day 28—N (%)	6 (25.0)	6 (25.0)	0 [– 0.24; 0.24]	1 [0.38; 2.66]	1.00
Days alive without life support and without organ failure [SOFA = 0] at Day 28	7.0 (5.0; 7.0)	7.0 (5.5;7.0)	0.21 [– 1; 1.4]		0.74
Days alive without vasopressors at Day 28—Median (IQR)	27.0 (16.0; 27.0)	27.0 (8.0; 27.0)	– 0.8 [– 6.7; 5.2]		0.87
Days alive without mechanical ventilation at Day 28—Median (IQR)	27.0 (18.5; 27.0)	27.0 (15.0; 27.0)	– 0.3 [– 6.0; 5.4]		0.93
Days alive without renal replacement therapy at Day 28—Median (IQR)	27.0 (17.5; 27.0)	27.0 (14.5; 27.0)	– 0.4 [– 6.1; 5.3]		0.79
Days alive and out of ICU at Day 28—Median (IQR)	18.0 (2.0; 23.0)	17.5 (0.0; 23.0)	– 0.5 [– 6.5; 5.5]		0.93
ICU length of stay—Median (IQR) days	5.0 (3.0; 10.0)	5.0 (3.0; 10.0)	0.6 [– 3.6; 4.7]		0.85
Hospital length of stay—Median (IQR) days	11.0 (8.0; 22.0)	12.0 (8.0; 18.0)	0.1 [– 5.2; 5.4]		0.97

which could justify higher fluid intake in patients in the control group and could also contribute to differences in fluid balance.

Another limitation of our trial was that the strict eligibility criteria led to excluding some of the most severe patients. The relatively low level of lactate at baseline suggests that the early acute phase of septic shock had already resolved. Therefore, our restriction protocol, particularly with regards to safety, should not be implemented in the first few hours of management of septic shock. A final point worth emphasizing is that the artificial nutrition part of the restriction protocol had no impact on cumulative fluid volume. This could be explained by the short duration of mechanical ventilation, during which patients received enteral nutrition, which prevented us from observing the impact of using a hyper-caloric, low-volume formula in the optimized restrictive strategy group.

Nevertheless, the study had several strengths. First, we targeted hidden fluid intake in contrast to previous studies. Second, the protocol permitted obtaining the lowest fluid balance on Day 5 ever published in a population of septic patients, without restricting the volumes of fluids used to manage hypoperfusion in the acute phase of septic shock, and without systematically using diuretics. Interestingly, the use of diuretics was lower in the intervention group, although this was not statistically significant. Third, all patients in the interventional group were able to comply with the protocol, suggesting that the optimized restrictive fluid strategy would be compatible for all patients in septic shock, regardless of severity. Finally, we did not observe more severe adverse effects in the optimized restrictive strategy group, especially severe hypernatremia and acute kidney injury KDIGO 3.

Although our pilot study did not achieve significance, considering the non-significant trend in fluid balance reduction in the optimized group (Fig. 2B), our approach to limiting fluid overload remains worth

Table 4 Adverse events

	Optimized restrictive strategy group (n = 24)	Control group (n = 24)	Absolute difference*	Relative risk*	*p*-Value
Metabolic disorders					
Frequency of mild hypernatremia (between 146 and 150 mmol/l)—N (%)	7 (29.2)	10 (41.7)	− 0.13 [− 0.39; 0.14]	0.7 [0.32; 1.53]	0.37
Frequency of severe hypernatremia (> 150 mmol/l)—N (%)	1 (4.2)	2 (8.4)	− 0.04 [− 0.18; 0.09]	0.5 [0.05; 5.15]	1.00
Frequency of hyponatremia (< 130 mmol/l)—N (%)	1 (4.2)	1 (4.2)	0 [− 0.11; 0.11]	1 [0.07; 15.08]	1.00
Renal function					
Frequency of hyperkalemia (> 6 mmol/l)—N (%)	0,0	0,0	0,0		–
Frequency of Acute Kidney Injury KDIGO2—N (%)	9 (37.5)	11 (45.8)	− 0.08 [− 0.36; 0.19]	0.82 [0.42; 1.61]	0.56
Frequency of Acute Kidney Injury KDIGO3—N (%)	3 (12.50)	7 (29.17)	− 0.17 [− 0.39; 0.06]	0.43 [0.13; 1.46]	0.16
Use of diuretics (cumulative dose administered over 7 days)—mg furosemide	40 (20; 160)	60 (30; 320)	− 31.9 [− 810.7; 746.9]	–	0.56
Nutritional issues					
Frequency of hypoglycemia (< 0.6 g/l)—N (%)	2 (8.4)	0 (0.00)	0.08 [− 0.03; 0.19]	–	0.49
Insulin use (cumulative dose administered over 7 days)—units	99.0 (6.0; 211.5)	84.5 (50.0; 129.00)	− 51.5 [− 152.0; 48.9]		0.73
Frequency of stage 3 pressure sores acquired in the ICU—N (%)	0 (0.0)	1 (4.2)	− 0.04 [− 0.12; 0.04]	–	1.00

*Adjusted values

exploring in a larger randomized controlled trial, perhaps in addition to other strategies such as early vasopressor use in the first 24 h of shock [10], limiting intravenous fluids in the absence of signs of severe hypoperfusion [11], and systematic use of diuretics [19]. An environmental and economic assessment would also be interesting. As we did not observe any harm to the patient, the additional savings made on unnecessary fluids would probably be advantageous for ecological and financial reasons.

Conclusions

In our pilot study, an optimized restrictive fluid strategy targeting hidden fluid intakes did not reduce the overall fluid balance at Day 5. However, the very low fluid balance obtained with the protocol and the unrepresentative control group, warrant further exploring this line of research in a larger randomized study.

Study protocol

The trial protocol, which includes the statistical analysis plan, was registered on ClinicalTrials.gov with the identifier NCT04947904.

For evaluation of patient safety, this trial was registered with France National Agency of Drug Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé, ANSM).

Trial data were monitored at the sites by independent monitors and monitored centrally by staff at the coordinating center. Statistical analyses were performed by the trial statistician in accordance with International Conference on Harmonisation Good Clinical Practice guidelines. The authors vouch for the accuracy and completeness of the reported analyses and for the fidelity of the trial to the protocol.

Abbreviations

ICU	Intensive Care Unit
SAPS II	Simplified Acute Physiology Score II
IQR	Interquartile range
KDIGO score	Kidney Disease Improving Global Outcomes
SOFA score	Sepsis-related Organ Failure Assessment

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05155-z.

Additional file 1.

Acknowledgements
We appreciate the interest of family members and patients in research, which enabled this trial. We thank research coordinators and physicians from all participating OPTIFLUID centers for their collaboration. We would like to thank Julie Pisano for help drafting the protocol, Christophe Masseguin for regulatory help, Loubna Elotmani, Audrey Ambert, Sabrina Ouberai, Sophie Lloret for data collection, and Sarah Kabani for editorial assistance. OPTIFLUID Investigators Dr Charlotte Danière, Dr Aurelien Daurat, Dr Geoffroy Dingemans, Dr Mikael François, Dr Nicolas Perin, Dr Eve Payan, Dr Remi Trusson, Dr Pauline Wyllinck; Clinical Pharmacist: Dr Hélène Poujol; Nimes University Hospital. Dr Lauren Beaudeau; Alès General Hospital

Author contributions
NB: Writing—Original Draft. CS: Methodology, Formal analysis. JPQ, NA, SG, AB, CR: Investigation, Validation. JYL, LM: Writing – review & editing, Supervision. SBD: Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Funding
This study was funded by an internal grant from the CHU de Nîmes.

Availability of data and materials
Principal data are provided within the manuscript or supplementary information files. The other data from this study are available upon reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the Comité de Protection des Personnes Sud-Méditerranée II (Number 2020-A01952-37). Written informed consent was obtained from patients or their legal surrogates.

Consent for publication
Written informed consent was obtained from patients or their legal surrogates either before randomization or as soon as possible thereafter.

Competing interests
The authors declare no competing interests.

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Received: 10 September 2024 Accepted: 31 October 2024
Published online: 21 December 2024

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